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Research Article

Modified Chitosan-Clay Nanocomposite as a Drug Delivery System Intercalation and *In Vitro* Release of Ibuprofen

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The present paper focused on the intercalation of ibuprofen into sodium montmorillonite, chitosan, and chitosan montmorillonite nanocomposites as a sustained release drug carrier. The compounds were characterized by X-ray diffraction (XRD), infrared spectroscopy (IR), thermogravimetric analysis (TGA), and transmission electron microscopy (TEM). The basal spacing of montmorillonite increased from 9.6 Å to 19.6 Å indicating the intercalation of modified chitosan and ibuprofen between lamellar layers. UV spectroscopy was employed to monitor the *in vitro* drug release processes in both pH 5.4 and 7.8 solutions. The results revealed that ibuprofen was released from MMT, CS, and Mod-CS/MMT steadily and was pH dependent.

1. Introduction

The need for safe, therapeutically effective, and patient compliant drug delivery systems continuously leads researchers to design novel tools and strategies. Clay minerals play a very crucial role in modulating drug delivery [1].

Ibuprofen (2-(p-isobutylphenyl) propionic acid) is a well-known hydrophobic oral nonsteroidal anti-inflammatory drug (NSAID) [2]. Ibyprofen has analgesic (pain-relieving) and antipyretic (fever-reducing) properties. It is particularly known for its use in pain relief from arthritis. However, it has a wide spectrum of gastrointestinal side effects ranging from mild dyspepsia to gastric bleeding. The gastric irritation is mainly due to the free carboxylic acid group in the chemical formula [3]. Due to its short plasma half life of 1–3 h following oral dosing and the gastric irritation, ibuprofen is an ideal candidate for preparing prolonged or controlled release drug products [3–11]. Since the property of reswelling is susceptible to the environmental pH, the incorporation of acid-sensitive drugs into the beads protects them from the gastric juice [12]. Therefore, drug-loaded alginate beads might provide these advantages for NSAIDs such as ibuprofen, which lead to gastric irritation. The formulation of ibuprofen as a controlled release dosage form of beads seems to be an important approach to overcome the potential problems in the gastrointestinal (GI) tract so as to achieve a reduction of the NSAID's adverse effects [13, 14].

Chitosan is a biocompatible, biodegradable, nontoxic, linear copolymer polysaccharide consisting of β (1-4)-linked 2-amino-2-deoxy-D-glucose (D-glucosamine) and 2-acetamido-2-deoxy-D-glucose (N-acetyl-D-glucosamine) units and has the structural similarity to cellulose (made up of β (1-4)-linked D-glucose units) [15]. Chitosan is the N-deacetylated derivative of chitin, although this N-deacetylation is never complete, which has a number of exposed amino groups making it polycationic polysaccharide. Depending on the amount/extent of deacetylation, different grades of chitosan are found. Due to its gel-forming property, it has been used in the designing of drug delivery system [15].

Montmorillonite (MMT) clay is one of the smectite groups, composed of silica tetrahedral sheets layered between alumina octahedral sheets. The imperfection of the crystal lattice and the isomorphous substitution induce a net negative charge that leads to the adsorption of alkaline earthmetal ions in the interlayer space. Such imperfection is responsible for the activity and exchange reactions with organic compounds. MMT also contains dangling hydroxyl end groups on the surfaces [16]. MMT has large specific surface area and exhibits good adsorption ability, cation exchange capacity,

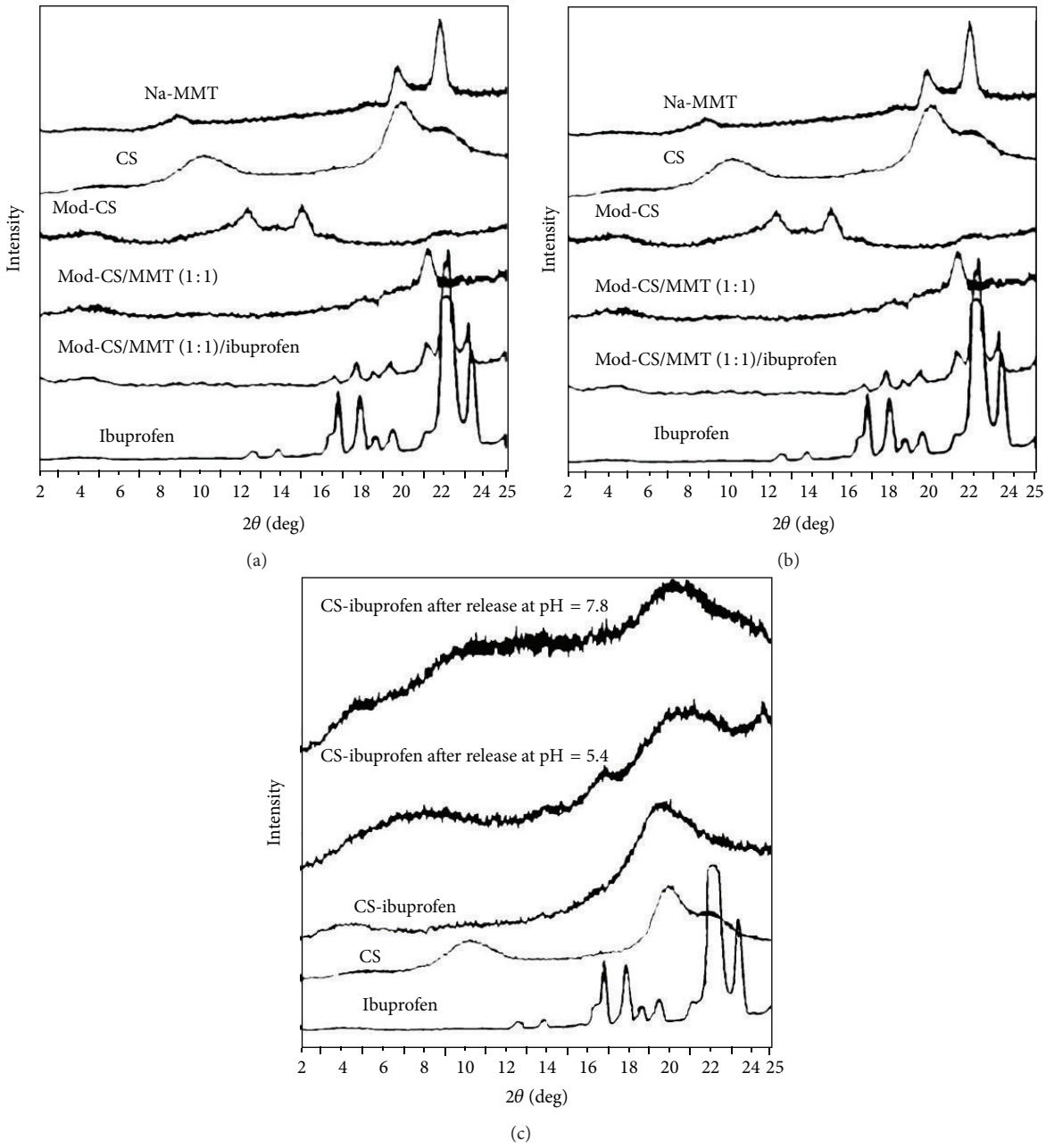

Figure 1: X-ray diffraction pattern of (a) Na-MMT, CS, mod-CS, mod-CS/MMT (1 : 1), ibuprofen, mod-CS/MMT—ibuprofen on cold. (b) Na-MMT, CS, mod-CS, and mod-CS/MMT (1 : 1), ibuprofen, mod-CS/MMT—ibuprofen on hot. (c) Ibuprofen, CS, and CS/ibuprofen after release at pH = 5.4 and 7.8.

standout adhesive ability, and drug-carrying capability. Thus, MMT is a common ingredient as both the excipient and active substance in pharmaceutical products [17]. The intercalation of organic species into layered inorganic solids provides a useful and convenient route to prepare organic-inorganic hybrids that contain properties of both the inorganic host and organic guest in a single material [18].

In recent years, smectite clays intercalated by drug molecules have attracted great interest from researchers since they exhibit novel physical and chemical properties [19].

In the present work, we successfully intercalate chitosan into layered silicate to prepare nanocomposite drug carrier that would alleviate some of the disadvantages of using clay. The cationic exchange mechanism involves interaction between Ph_3P^+ groups of modified CS and negatively charged sites in the clay structure. The resulting materials were characterized by IR, XRD, and TEM. The release rate of ibuprofen from the nanocomposites, Na-MMT, and CS was investigated.

2. Characterization of Organoclay/Drug

2.1. XRD Spectra. The XRD patterns of Ibuprofen, Na-MMT, chitosan, mod-CS/MMT (1 : 1), mod-CS/MMT (1 : 1)/ ibuprofen, Na-MMT/ibuprofen, and CS/ibuprofen are shown in Figures 1(a)–1(c). Pure ibuprofen exhibits typical reflection

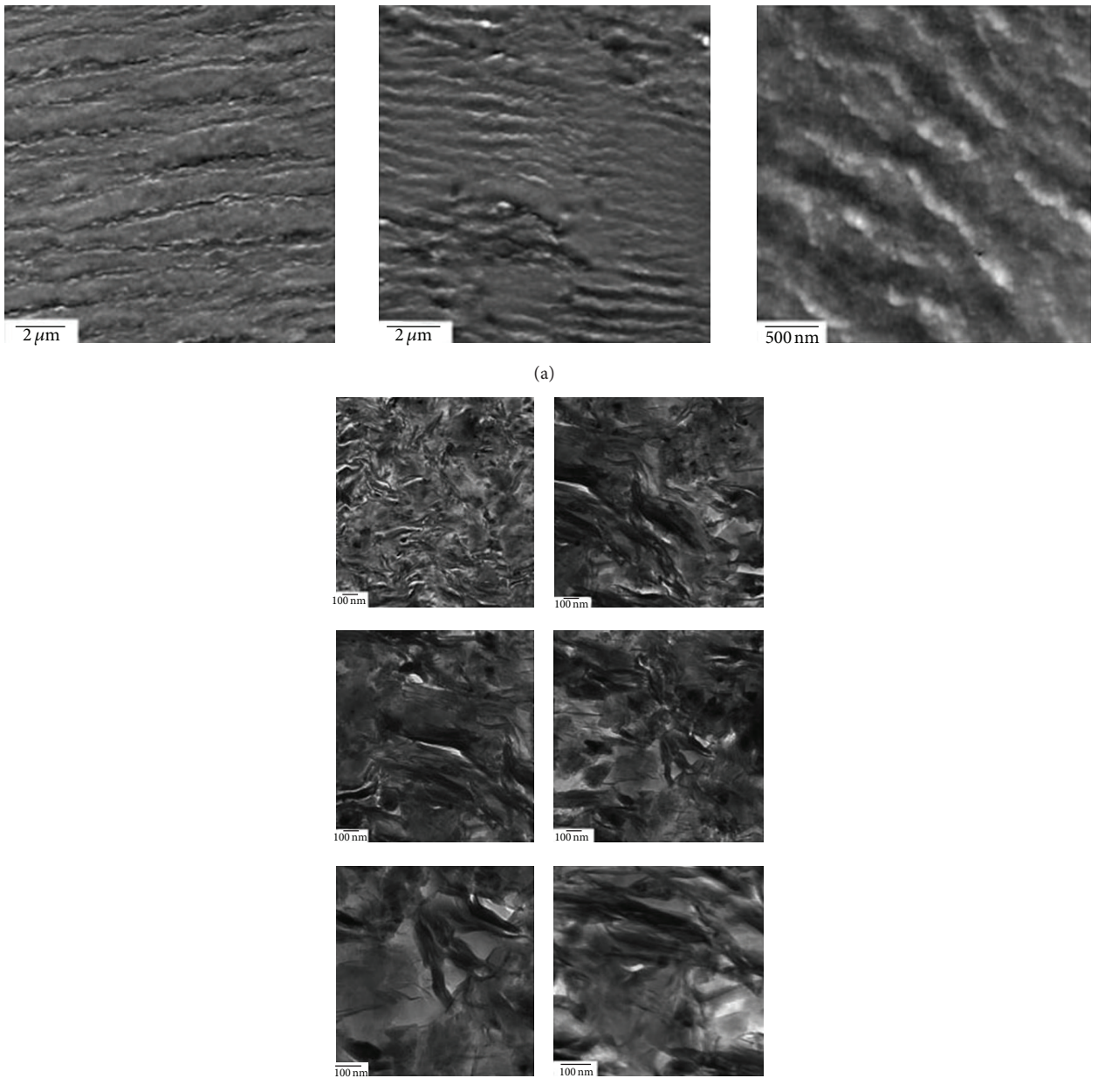

Figure 2: TEM micrographs of (a) M. chitosan-MMT/ibuprofen (1 : 1) on cold and (b) M. chitosan-MMT/ibuprofen (1 : 1) on hot.

at $2\theta = 6.06^{\circ}$, 16.65°, and 22.28°. Na-MMT exhibits typical reflection at $2\theta = 9.6^{\circ}$ corresponding to d_{001} is 9.6 Å. CS shows the characteristic crystalline peaks around $2\theta = 10$, 20, and 22°. The peaks around 10 and 20 are related to crystal (1) and crystal (2) in chitosan, respectively. The unit cell of crystal (1) is characterized by $a = 7.76, b = 10.91, c = 10.30$ Å, and $\beta = 90^{\circ}$ and it is larger than that of crystal (2) whose unit cell is characterized by $a = 4.4$, $b = 10.0$, $c = 10.3$ Å, and $\beta = 90^{\circ}$ [20–22]. After modification of chitosan, mod-CS showed two sharp peaks at $2\theta = 12$ and 15° and a broad peak at ~22°. This indicates that mod-CS formed a new crystallite. In mod-CS/MMT (1 : 1) the d_{001} peak of the clay has disappeared and a broad peak at $2\theta = 4^{\circ}$ appeared corresponding to an increase in d-spacing. This increase in basal spacing is attributable to the intercalation of polymer chain inside the clay layers. The low peak intensity in the nanocomposite is because of the decrease in the coherent layer scattering.

The XRD of the nanocomposite formed after loading ibuprofen on Na-MMT, chitosan, mod-CS/MMT (1 : 1) showed peaks characteristic for both ibuprofen and support. the intensity of the (001) reflection the intercalation of ibuprofen.

2.2. TEM Result. TEM of a thin film of mod-CS/MMT (1 : 1) ibuprofen (solvent method on cold) and mod-CS/MMT (1 : 1) ibuprofen (solvent method on cold) are shown in Figures 2(a) and 2(b), respectively. Figure 2(a) shows that silicate layers

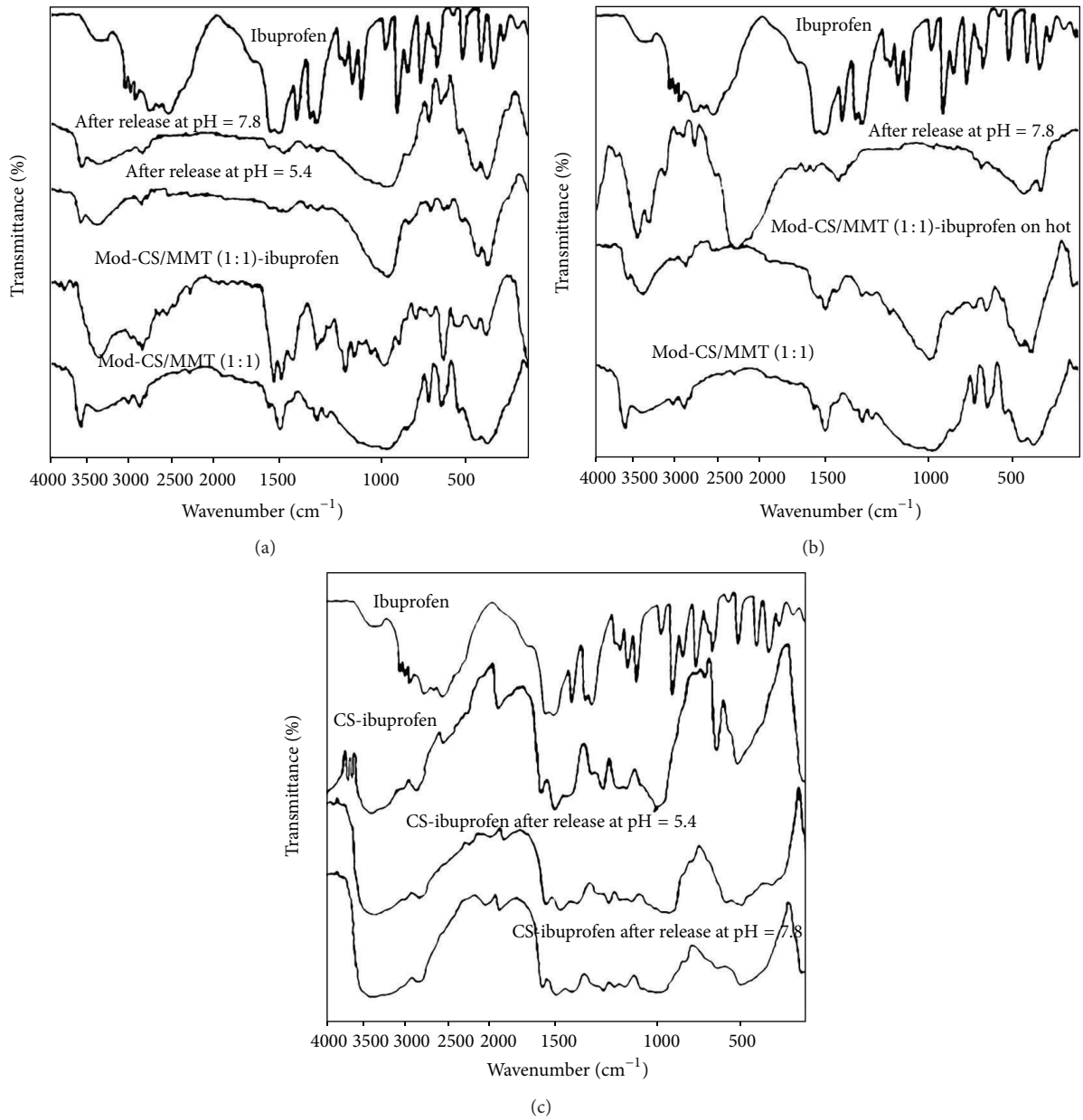

Figure 3: IR spectra in the region 4000–400 cm^{-1} of (a). Na-MMT, CS, mod-CS, mod-CS/MMT (1 : 1), ibuprofen, mod-CS/MMT—ibuprofen on cold. (b) Na-MMT, CS, mod-CS, mod-CS/MMT (1 : 1), Ibuprofen, mod-CS/MMT—Ibuprofen on hot. (c). Ibuprofen, CS, CS/ibuprofen and after release at pH = 5.4 and 7.8.

remain in exfoliated structure in mod-CS/MMT (1 : 1) ibuprofen on cold. However, it is observed that few layers remain in intercalated structure in mod-CS/MMT (1 : 1) ibuprofen prepared by solvent method on hot. This is consistent with the conclusion drawn from XRD.

2.3. IR Spectrum. The IR spectrum in Figures 3(a)–3(c) of ibuprofen the strong carbonyl absorption band at 1721 cm^{-1}, the bands between 3700 and 3100 cm^{-1} are related to the aromatic ring. The bands between 3000 and 2800 cm^{-1} are the alkyl stretching vibration of ibuprofen. For Na-MMT, the characteristic absorption band at 3632 cm^{-1} [ν (O–H)] is assigned to the stretching vibration of Al–OH. The symmetrical Si–O–Si band [ν (Si–O–Si)] is characterized by the stretching band at 1160 cm^{-1}. Other characteristic adsorption bands of pure clay mineral are at 914 [δ (Al–Al–O)], 886 [δ (Al–Fe–O)], and 848 cm^{-1} [δ (Al–Mg–O)]. IR spectrum of CS shows a broad band at 3462 cm^{-1} corresponding to the stretching vibration of N–H. The peaks at 2937 and 2857 cm^{-1} are typical of C–H stretching vibration, while peaks at 1660, 1551, and 1309 cm^{-1} are characteristic of amides I, II, and III, respectively. The sharp peaks at 1442 and 1374 cm^{-1} are assigned to the CH_3 symmetrical deformation mode and 1036 cm^{-1} is indicative of C–O stretching vibration [ν (C–O–C)]. The small peak at ~798 cm^{-1} corresponds to wagging of the saccharide structure of CS. The IR spectrum of

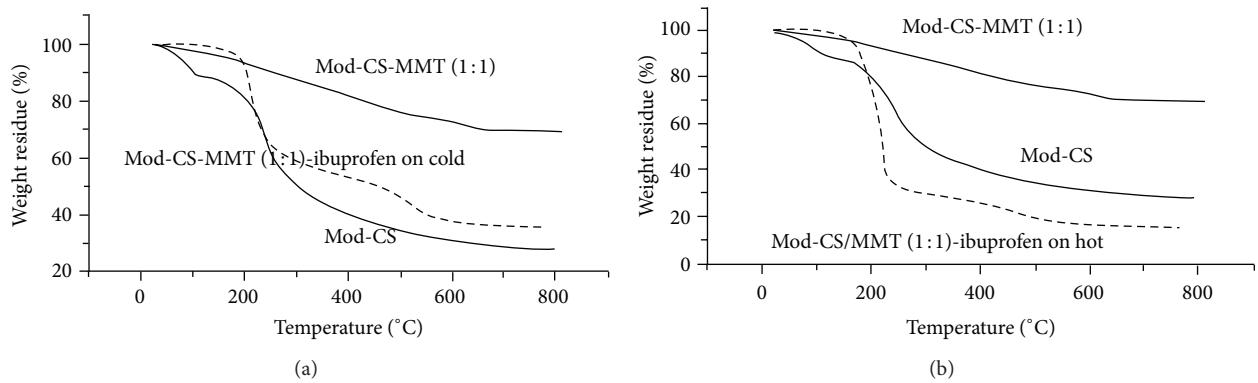

Figure 4: TGA of mod-CS, mod-CS/MMT (1:1), and mod-CS/MMT—ibuprofen prepared by solvent method (a) on cold and (b) on hot.

mod-CS shows bands at 1740 and 1615 cm^{-1} corresponding to C=O stretching vibration and NH–, respectively. The bands at 1421 (m), 1164 (m), and 1063 cm^{-1} (w) correspond to phosphonium salt attached to Ph group. Not all characteristic bands belonging to MMT and ibuprofen appear in the spectrum of ibuprofen/MMT; several new absorption bands at 2390 and 1558 cm^{-1} are also recognized. This also indicates that ibuprofen interacts strongly with the montmorillonite layers.

2.4. Thermal Stability. Montmorillonite shows two distinct steps. The first one of about 7% at 48–120°C is due to the free water evaporation. The second weight loss at 550–720°C is due to the structural dehydration [23]. In TGA curves (Figure 4) of mod-CS, mod-CS-MMT, and mod-CS-MMT\ibuprofen, weight loss at 100 to 400°C corresponds to the decomposition of ibuprofen. Other weight losses are the same as those of MMT. The TGA curve of mod-CS-MMT\ibuprofen on cold with an initial concentration of 0.3 mmol/g (drug-loaded amount 36.09 wt.%) while mod-CS-MMT\Ibuprofen on hot with the same initial concentration (drug-loaded amount 15.12 wt.%) shows a sharp weight loss at around 471°C due to the decomposition of intercalated ibuprofen.

2.5. Drug Release Response. The drug release response from mod-CS/MMT nanocomposite in buffer solution with two different pH values, 5.4 as example for stomach pH and 7.4 for colon, was studied at the physiological temperature of 37°C (Figures 5(a)–5(c)). The swellability of the carrier in the buffer solution The swelling ratio for mod-CS/MMT (1:1) in table indicate that the great swellability the greater the release is shown in Table 1.

Ibuprofen, a relatively weak acidic drug, was intercalated into mod-CS/MMT and CS. The *in vitro* release experiment showed that the release of ibuprofen from mod-CS/MMT\ibuprofen and CS\ibuprofen was affected by the pH value of the dispersion. The release rate in simulated intestinal fluid (pH = 7.4) was noticeably higher than that in simulated gastric (pH = 5.4). The release of ibuprofen from ibuprofen/MMT was affected by the pH value of the dispersion. The release rate in simulated intestinal fluid (pH = 7.4) was noticeably higher than that in simulated gastric (pH = 1.2). The results indicate that MMT can be used as the sustained-release carrier of IBU in oral administration. The results indicate that mod-CS/MMT can be used as the sustained-release carrier of ibuprofen in oral administration which allows minimum effective dose to be delivered locally and prolongs the duration of drug activity, thus improving the therapeutic efficacy and decreasing side effects by minimizing the transportation of the drug to the systemic circulation against inflammation [24] which minimizes the adverse effect of oral administration and avoids contact between the drug and the gastric mucosa [25].

Table 1: Swellability of the carriers in different pH buffer solutions. Swellability wt%.

Code of nanocomposite	Wt at pH = 7.8	Wt at pH = 5.4
Mod-CS/MMT (1:1)-ibuprofen on hot	3.05×10^{-5}	2.31×10^{-5}
Mod-CS/MMT (1:1)-ibuprofen on cold	2.77×10^{-5}	1.25×10^{-5}
CS-ibuprofen	50.7×10^{-5}	83.4×10^{-5}

2.6. Characterization of the Support after Release. The drug carrier nanocomposites were further subjected to examination by IR and XRD after drug release. The IR spectra of mod-CS/MMT/ibuprofen after release Figure 3 indicates that the peaks characteristic to mod-CS, Ibuprofen disappeared and bands characteristic to Na-MMT is observed. These observations suggest that the drug release occurred by degradation of the nanocomposites. XRD of samples after release has no visible diffraction peak within the measured range. The peak at $2\theta \approx 20^{\circ}$ appearing in all the diffraction patterns corresponding to the crystallographic plans (110) and (020) of the clay layers disappeared after release and an amorphous structure is obtained as in Figure 6 especially after immersion of the carrier at pH 7.8.

3. Experimental

3.1. Materials. Chitosan from a shell of *Chionoecetes opilio* has 70% degree of deacetylation with average molecular

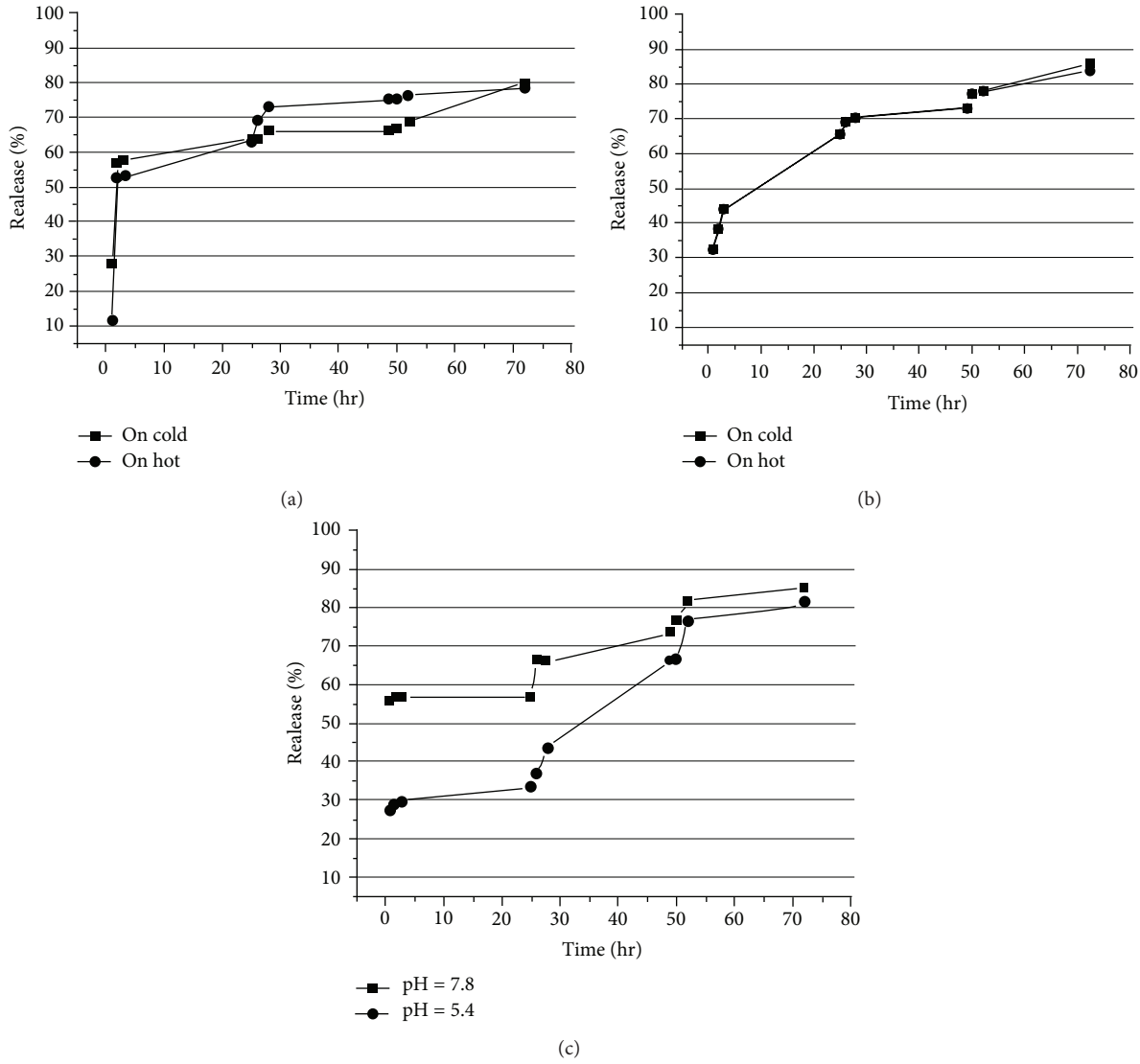

Figure 5: *In vitro* ibuprofen release in phosphate buffer solution at (a) pH = 7.8, and (b) pH = 5.4 at 37°C. ((a)-(b)) Mod-CS/MMT—ibuprofen (1 : 1) by different method. (c) CS/ibuprofen.

weight of 400.000 and was purchased from Aldrich chemicals. Ibuprofen, triphenyl phosphine, and chloroacetyl chloride were provided from Aldrich chemicals. The clay mineral used in this study was sodium montmorillonite (Colloid BP) from Southern Clay Products Inc. (Gonzales, TX, USA) with cation exchange capacity (CEC) of 114.8 meq/100 g. The structure of CS and ibuprofen is shown in Figure 7.

3.2. Chloroacetylation of Chitosan. 75.2 mL (99.6 mmol) of pyridine was added to 1 g of chitosan. The mixture was cooled in an ice-salt bath and chloroacetyl chloride (7.965 mL, 99.6 mmol) was added dropwise with stirring. The reaction mixture was stirred overnight at 40°C for three days. The chloroacetylated chitosan was precipitated by addition of diluted HCl (1 N), filtered off, and washed with distilled water several times and the product was dried to give 0.95 g.

3.3. Synthesis of Triphenyl-Chloro Acetylated Chitosan Phosphonium Salt (mod-CS). 2 g of chloroacetylated chitosan was dissolved in 20 mL of dry DMF followed by addition of 5.33 g (20 mmol) of triphenyl phosphine. The reaction mixture was stirred for four days at 80°C in an oil bath. The product was filtered off and washed with DMF to give 1.5 g.

3.4. Preparation of Triphenyl-(Chloroacetylated Chitosan) Phosphonium Salt-Montmorillonite Intercalates (mod-CS/MMT). 1 g of Na-MMT was swelled in 30 mL of water by stirring overnight at 40°C. After swelling of clay, 1 g mod-CS dissolved in 10 mL DMF was added and stirred for 24 hr. The product (mod-CS/MMT (1 : 1)) was filtered, washed several times with water, and collected by a filter press, and dried at 80°C in vacuum oven for 10 hr.

3.5. Loading of Ibuprofen by Solvent Method

3.5.1. Loading of Ibuprofen on Modified Chitosan. 0.3 g ibuprofen in 10 mL DMF was added to 0.5 g of mod-CS/MMT (1 : 1) and was swelled in 30 mL DMF with stirring for 24 hr.

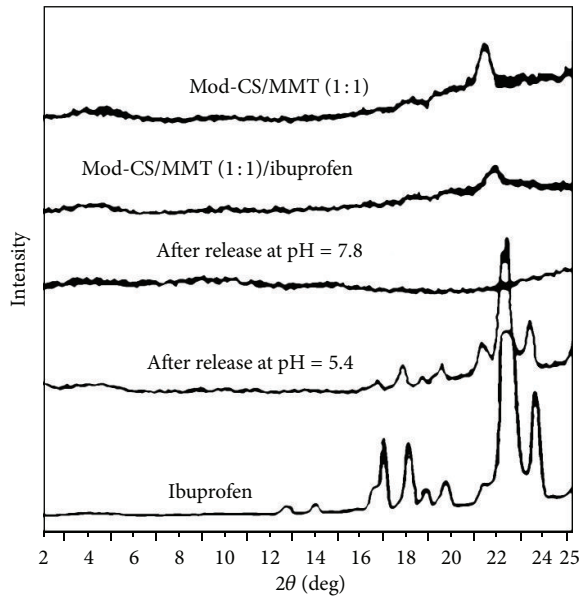

Figure 6: X-ray diffraction pattern of mod-CS, mod-CS/MMT (1 : 1), ibuprofen, and mod-CS/MMT—ibuprofen on cold after release.

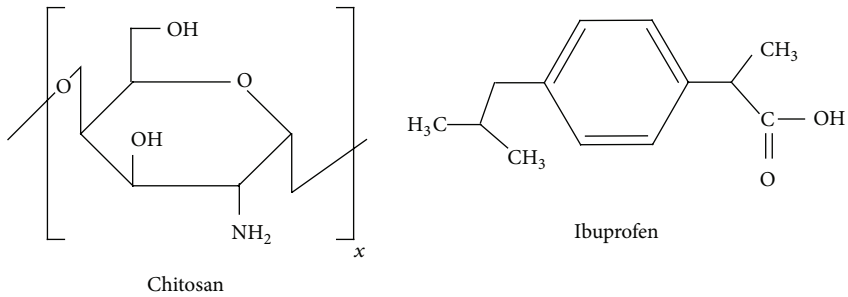

Figure 7: Structure of CS and ibuprofen.

The product was filtered, washed several times with water, collected by a filter press, and dried at 80°C in vacuum oven for 10 hr. The same procedure was done by applying temperature (80°C) to improve the absorption between the drug and Mod-CS.

3.5.2. Loading of Ibuprofen on Na-MMT. 1 g of Na-MMT was swelled for 48 hrs at 40°C in DMF. Then, 5 g of ibuprofen dissolved in DMF was added. The reaction mixture was further stirred for another 24 h at 40°C. The product (Na-MMT/ibuprofen) was collected by filtration and washed with ethanol (three times) to remove the excess of unloaded drug and dried under vacuum at 40°C overnight.

3.5.3. Loading of Ibuprofen on CS. 1 g of CS was dissolved in 2% acetic acid. Then, 0.3 g of ibuprofen dissolved in 10 mL DMF was added. The reaction mixture was further stirred for another 24 h at 40°C. The product (CS-ibuprofen) was collected by filtration and washed with ethanol (three times) to remove the excess of unloaded drug and dried under vacuum at 40°C overnight.

3.6. Drug Release

3.6.1. Preparation of Phosphate Buffer (PB) Solution. Phosphate buffer solution (PB) was prepared by dissolving sodium phosphate dibasic (21.7 g) and potassium phosphate monobasic (2.6 g) in 1 L deionized water and the pH was adjusted to 5.4 and 7.8 using 0.1 N sodium hydroxide or 0.1 N hydrochloric acid, respectively.

3.6.2. In Vitro Drug Release. The drug release responses of CS, Na-MMT, and mod-CS/MMT drug carriers were studied at the physiological temperature of 37 ± 0.5°C and pH 5.4 and 7.8. The pH values of 5.4 and 7.8 were selected to closely mimic the pH gradient from the stomach to the intestine. In each experiment, 10 mg of the drug carriers was submerged in 50 mL of buffer solution. An aliquot of the release medium (3 mL) was withdrawn at regular time for 72 h. The content of ibuprofen in buffer solution was quantified using UV-VIS spectrophotometry at λ_{max} = 265 nm. After each measurement, the withdrawn was put back into the system. Given that the measurement time was very short, while the predetermined drug release time interval was significantly

larger, the influence of the returned medium on drug release during the measurement time was insignificant. All the drug release experiments were repeated three times and the average was calculated.

3.6.3. Swelling Measurements. The samples were weighed in a sintered glass, W_1, and immersed in buffer solution (pH = 5.4 and 7.8) at 37°C. The samples were centrifuged to remove the surface buffer solution and reweighed immediately, W_2. The process was repeated at the same time intervals used in the measurement of *in vitro* drug release. The swellability percentage was calculated using the formula $(W_2 - W_1/W_1) \times 100$.

4. Conclusions

Modified chitosan/MMT nanocomposite was successfully synthesized. It entails two steps: modification of chitosan by chloroacetylation and formation of phosphonium salt, which is then chemically intercalated to MMT through an ion exchange process. The resulting nanocomposite was used as support for ibuprofen. The release of ibuprofen from the support is affected by the drug loading capacity, the percentage of CS in the nanocomposite, the pH of the medium, and the morphology of the nanocomposites, which is affected by the method of preparation. The drug loaded chitosan and mod-chitosan can be of immense importance in the drug delivery through the oral rout as well as the other routes as sustained and controlled release dosage forms. The desired effects in the drug release and the therapeutic value can be obtained by intercalated ibuprofen at different temperature. As chitosan is nontoxic, biodegradable, and biocompatible, it can be used for the delivery of the ibuprofen in controlled and sustained release manners.

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